PAFAH1B1-associated Lissencephaly/Subcortical Band Heterotopia: PAFAH1B1 Gene Deletion/Duplication

**Condition Description**

PAFAH1B1-associated lissencephaly/subcortical band heterotopia (SBH) includes Miller-Dieker syndrome (MDS) and isolated lissencephaly sequence (ILS). During embryogenesis, reduced levels of neuronal migration cause the cortical malformations, lissencephaly and SBH. Lissencephaly refers to a "smooth brain" with absent gyri or abnormally wide gyri. SBH refers to a band of heterotopic gray matter located beneath the cortex but separated from it by a thin layer of normal white matter. MDS is characterized by lissencephaly, distinctive facial features, and severe neurological abnormalities. ILS is characterized by lissencephaly, which leads to developmental delay, intellectual disability, and seizures.

Mutation of the PAFAH1B1 (17p13.3) gene, previously known as the LIS1 gene, cause PAFAH1B1-associated lissencephaly/subcortical band heterotopia. MDS is caused by deletions that include both the PAFAH1B1 and the YWHAE genes. ILS is caused by mutation of the PAFAH1B1 gene with ~68% of mutations being detected by deletion/duplication analysis and ~32% being detected by sequencing analysis.

Please note that lissencephaly and SBH are graded by anterior-posterior gradient and severity. When the lissencephaly or SBH is more severe posteriorly, it is referred to as a posterior to anterior (p>a) gradient. When more severe anteriorly, it is referred to as an anterior to posterior (a>p) gradient. PAFAH1B1 abnormalities generally give rise to a p>a gradient, whereas abnormalities of DCX generally give rise to an a>p gradient (GeneReviews). This testing is for the PAFAH1B1 gene only.

For patients with suspected PAFAH1B1-associated lissencephaly/subcortical band heterotopia, deletion/duplication analysis is recommended as the first step in mutation identification. For patients in whom mutations are not identified by deletion/duplication analysis, full gene sequencing is appropriate.

**References:**

- GeneReviews
- OMIM #601545: PAFAH1B1 gene
- OMIM #607432: Lissencephaly 1

Deletion/Duplication testing should be ordered as the first tier test.

**Genes**

LIS1, PAFAH1B1

**Indications**

This test is indicated for:

- Confirmation of a clinical diagnosis of PAFAH1B1-Associated Lissencephaly/Subcortical Band Heterotopia.
- Carrier testing in adults with a family history of PAFAH1B1-Associated Lissencephaly/Subcortical Band Heterotopia.

**Methodology**

DNA isolated from peripheral blood is hybridized to a CGH array to detect deletions and duplications. The targeted CGH array has overlapping probes which cover the entire genomic region.

Please note that a "backbone" of probes across the entire genome are included on the array for analytical and quality control purposes. Rarely, off-target copy number variants causative of disease may be identified that may or may not be related to the patient's phenotype. Only known pathogenic off-target copy number variants will be reported. Off-target copy number variants of unknown clinical significance will not be reported.

**Detection**

100% of MDS will be detected by deletion/duplication analysis. 68% of ILS will be detected by deletion/duplication analysis. Detection is limited to duplications and deletions. The CGH array will not detect point or intronic mutations. Results of molecular analysis must be interpreted in the context of the patient's clinical and/or biochemical phenotype.

**Specimen Requirements**

Submit only 1 of the following specimen types

* Preferred specimen type: Whole Blood

**Type: Whole Blood**
Specimen Requirements:

In EDTA (purple top) or ACD (yellow top) tube:
Infants (2 years): 3-5 ml
Older Children & Adults: 5-10 ml

Specimen Collection and Shipping: Refrigerate until time of shipment. Ship sample within 5 days of collection at room temperature with overnight delivery.

**Type: Saliva**

Specimen Requirements:

Oragene™ Saliva Collection kit (available through EGL) used according to manufacturer instructions.

Specimen Collection and Shipping: Store sample at room temperature. Ship sample within 5 days of collection at room temperature with overnight delivery.

**Related Tests**

- Sequence analysis of the *PAFAH1B1* gene is available for those individuals in whom deletion/duplication analysis is negative.
- Both sequencing (SO) and deletion/duplication (SQ) analysis of the *DCX* gene is available.
- Custom diagnostic mutation analysis (KM) is available to family members if mutations are identified by targeted mutation testing or sequencing analysis.
- Prenatal testing is available only for known familial mutations to individuals who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.